Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 18 April 2009, Revised 3 June 2009, Accepted 4 June 2009 Published online 15 July 2009 in Wiley Interscience

(www.interscience.wiley.com) DOI: 10.1002/jlcr.1654

Syntheses of three stable isotope-labeled ethylcyclopropanes

John E. Baldwin* and Edward J. O'Neil

Three stable isotope-labeled ethylcyclopropanes have been synthesized in preparation for a mechanistic study of its fragmentation to methane and butadiene. Two tactical innovations have been used to deal with practical synthetic challenges posed by the very limited solubility of methylmagnesium iodide in tetrahydrofuran and the high volatility and high tendency to form aerosols characteristic of ethylcyclopropane.

Keywords: (2-^{13}C-1-ethyl)cyclopropane; (2-d_3-1-ethyl)cyclopropane; 2,2-d_2-1-ethylcyclopropane; thermal fragmentation of ethylcyclopropane to methane and butadiene

Introduction

Over the years following the discovery in 1896 of the thermal rearrangement of cyclopropane to propylene by Tanatar [1] – the first chemical reaction recognized to be effectuated by heat alone, rather than be dependent on the participation of another chemical [2] – many similar isomerizations were documented. In the pattern of this paradigm, many alkyl-substituted cyclopropanes led to structural isomers formally reached through homolytic cleavage of a cyclopropyl C–C bond to give a 1,3-trimethylene diradical. This short-lived diradical could revert to the cyclopropane starting material or react further through shifting a hydrogen from C(2) to C(1) or C(3). Methylcyclopropane gave rise to 1-butene, *cis*- and *trans*-2-butene, and isobutylene (2-methyl-1-propene).[3] Ethylcyclopropane (**1**) in the gas phase at 454–484°C formed 1-pentene, *cis*- and *trans*-2-pentene, and 2-methyl-1-butene.[4] 1,1-Diethylcyclopropane (**3**) was isomerized at 425–475°C to 3-ethyl-1-pentene and 3-ethyl-2-pentene.[5] Numerous similar rearrangements of cyclopropanes substituted with one or more alkyl groups or deuterium labels or both have been recorded. Additional examples no longer occasion any surprise.

What was not at all anticipated in 1965 was the independent and nearly simultaneous discoveries of the thermal conversions of ethylcyclopropane (**1**) to methane and butadiene (**2**) [4] and 1,1-diethylcyclopropane (**3**) to 2-ethylbutadiene (**4**).[5] These reactions appeared to be homogeneous unimolecular parallel processes and constituted fair proportions, about 20%, of the overall conversions of starting materials to products.

These reactions were clearly 'of a type previously not reported'. Mechanistic possibilities were cautiously formulated by the authors, [4,5] and other contrasting perspectives were shared soon thereafter.[6] But no mechanistic clarifications were sought soon thereafter or have been pursued through experimental or theoretical approaches over recent decades. Halberstadt and Chesick noted in 1965 that pyrolysis of a mixture of **1** and **1**-d_{10} followed by analysis of the methane produced through MS could unambiguously test between a molecular mechanism versus one involving free-radical intermediates such as CH_3 and $CH_2=CH–CH_2CH_2$[4] (Scheme 1).

Yet such an experiment or any other isotope-labeling-dependent search for mechanistic insights for the **1**→**2** and **3**→**4** fragmentations has not been reported. The reaction has just been disregarded and overlooked. As an instance, the authoritative and nearly indispensable compendium of kinetic results for thermal unimolecular reactions compiled by Willcott *et al.* published in 1972 listed the isomerizations of ethylcyclopropane and 1,1-diethylcyclopropane to isomeric acyclic monoolefins, but it did not include the strikingly anomalous fragmentations forming methane and **2** or **4**. [7] For reactant **3**, the compendium cited the activation parameters leading to the isomeric olefins exactly right, but recorded only one of the three thermal reaction product structures accurately.

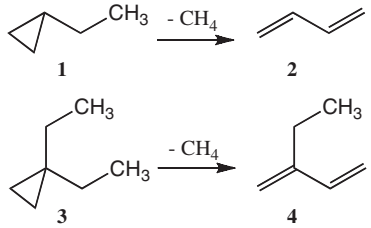
To take up the mechanistic uncertainties continuing to shroud these fragmentation reactions, screening them from intellectual or active research attention, we in collaboration with Lewis and his colleagues [8] have committed to take up the issues they raise through studying the thermal reactions of isotopically labeled ethylcyclopropanes under single-pulse shock-tube reactor conditions so as to obviate complications associated with wall effects. The present work reports the syntheses of three isotopomers of **1**: carbon-13 methyl-labeled ethylcyclopropane (**1**-^{13}**C**), the d_3-methyl-labeled analog (**1**-d_3), and 2,2-d_2-1-ethylcyclopropane (**1**-d_2).

Results

Synthetic strategies suitable for making these compounds were easily envisaged, for apt isotopically labeled precursors were readily available and no stereochemical issues were of concern.

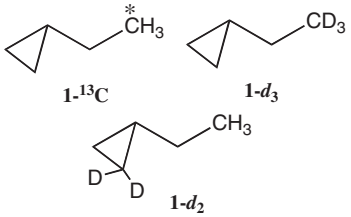
Department of Chemistry, Syracuse University, Syracuse, NY 13244, USA

**Correspondence to: John E. Baldwin, Department of Chemistry, Syracuse University, Syracuse, NY 13244, USA.*
E-mail: jbaldwin@syr.edu



Scheme 1. Methane from thermal fragmentations of ethylcyclopropane and 1,1-diethylcyclopropane.

Nevertheless, successful preparations of these three isotopomers took some time to realize.

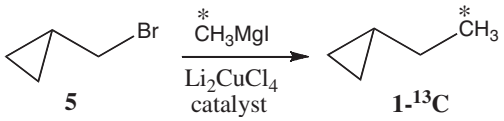


The obvious route to **1-^{13}C** was to couple $^{13}CH_3MgI$ with (bromomethyl)cyclopropane (**5**) in the presence of the catalyst dilithium tetrachlorocuprate(II).[9] Similarly, CD_3MgI in place of $^{13}CH_3MgI$ should lead to **1-d_3** (Scheme 2).

Diethyl ether (b.p. 34.6°C), an excellent solvent for preparing CH_3MgI, was not appropriate for dealing with an ethereal solution of ethylcyclopropane (b.p. 36.2°C).[10] The same conclusion was reinforced through experiments with capillary and preparative GC trials with ether and **1**. They were of essentially identical chromatographic characteristics on a variety of columns. Anticipating using Li_2CuCl_4 as a catalyst for a coupling reaction between a labeled CH_3MgI and **5**, aware that the catalyst is available commercially as a 0.1 M solution in THF, and conscious of the widely recognized reputation THF enjoys as a particularly useful reagent for preparing Grignard reagents from alkyl halides, it seemed one could prepare $^{13}CH_3MgI$ or CD_3MgI in THF, then continue on with the coupling reaction by adding dilute Li_2CuCl_4 in THF and (bromomethyl)cyclopropane to the THF solution of the isotopically labeled Grignard reagent. This approach starting with CH_3I, Mg, and dry THF as solvent failed totally. The reaction mixture appeared as a gray mud, not a typical Grignard reagent preparation conducted in ether.

After some reflection, the difficulty was inferred to derive from a lack of solubility of CH_3MgI in THF. There are reported cases where relatively insoluble alkyl Grignard reagents such as solid CH_3MgI (m.p. 84–86°C; presumably $CH_3MgI(THF)_2$) [11] will dissolve in such co-solvents as benzene or xylene.[11,12] This lead prompted preparing CH_3MgI in dibutyl ether[13] and then counting on the Grignard reagent to remain in solution when diluted modestly with Li_2CuCl_4 in THF. This stratagem worked: the Grignard reagent was prepared in the usual fashion in dibutyl ether, and the solution of the reagent, diluted by a four-fold lesser volume of the THF solution of catalyst, allowed it to remain in solution. The coupling reaction leading to the ethylcyclopropane product was then realized.

Separation of **1** or a labeled version of **1** from THF (b.p. 65–67°C) and dibutyl ether (b.p. 142–143°C) after work-up was achieved through fractional distillation followed by a final purification by preparative GC on a β,β'-oxydipropionitrile (ODPN) column. The GC separation of **1** and THF was complete



Scheme 2. Catalyzed cross-coupling of (bromomethyl)cyclopropane with $^{13}CH_3MgBr$.

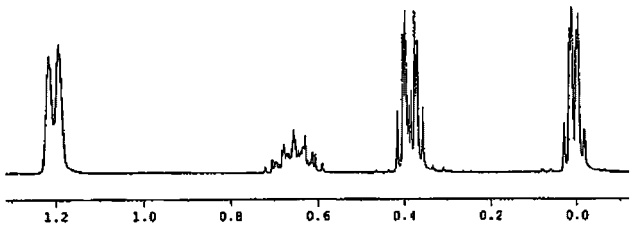


Figure 1. The proton NMR spectrum of **1-d_3**. The conspicuous methyl triplet centered at δ 0.97 for ethylcyclopropane is simply absent.

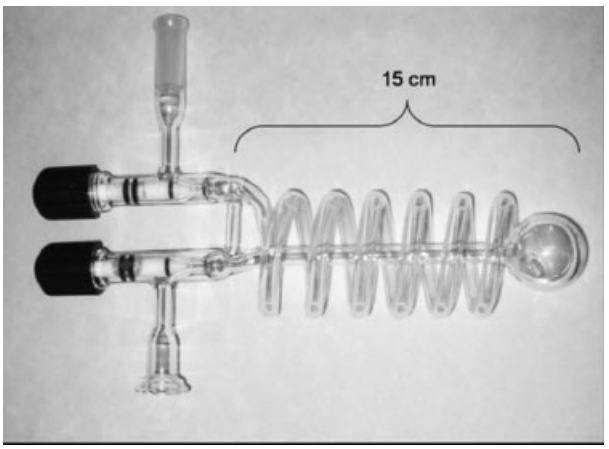


Figure 2. Collection vessel for preparative GC samples.

and efficient. The next challenging aspect of the process turned out to be the collection of the hydrocarbon without serious losses associated with aerosol issues. Condensing **1** as it passed from the heated thermal conductivity detector block into a typical collection tube was seriously inefficient. A more suitable collection device proved excellent. Both the design of the glassware and stopcocks and the cooling bath prepared from pentane and liquid nitrogen held at −131°C contributed to the successful outcome. The low-temperature bath, a less common cryogenic fluid than liquid nitrogen (b.p. −196°C) at this temperature range, captured the product without hazarding collecting liquid oxygen (b.p. −183°C) before transferring and sealing samples for storage or transport. The purified samples of **1-^{13}C** and **1-d_3** were secured in better that 98+% purity.

The success of a collection of **1-d_3** is mirrored in Figure 1. An image of the collection device utilized is provided in Figure 2. The O-ring seal joint connection shown in Figure 2 links through a 3-way stopcock having a PTFE plug with an oblique bore to the carrier gas flow from the GC detector to the collector or to the vent, thus facilitating an easy switch; the other connector accommodates a drying tube. When the collection is complete, both stopcocks are closed, the sample is taken to a vacuum line, and it is fitted to one of the connections for transfer as required on the line.

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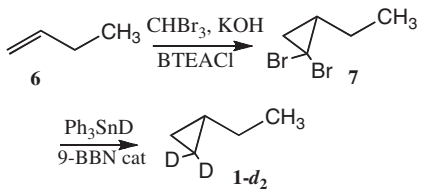

Scheme 3. Preparation of 2,2-d_2-1-ethylcyclopropane.

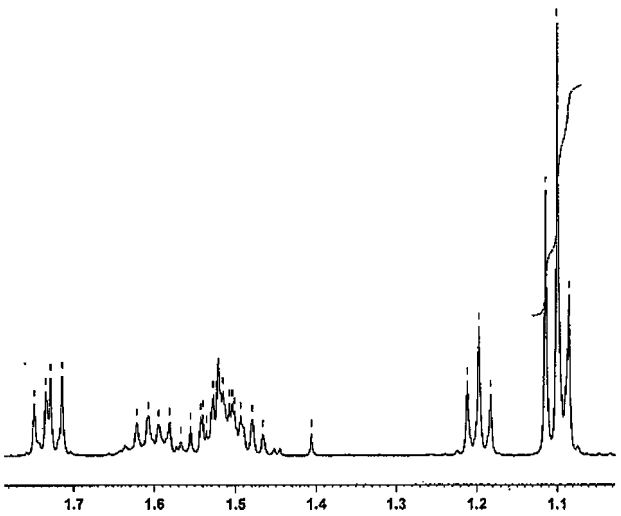

Figure 3. The proton NMR spectrum of **7**. The geminal protons at C3 are centered at δ 1.73 and 1.20.

The synthetic route to **1**-d_2 progressed from 1-butene (**6**) to 2,2-dibromo-1-ethylcyclopropane (**7**) and on to its reduction with Ph_3SnD to afford **1-d_2** (Scheme 3).

The addition of dibromocarbene to 1-butene was reported in 1971.[14] Dibromide **7** was then obtained in 11.4% yield in fair homogeneity, with $CHBr_3$ as the major impurity. No other synthesis of **7** has been published more recently. In the present work an alternative protocol was utilized: 1-butene (**6**) was combined with CBr_2 prepared from $CHBr_3$ and KOH pellets in anhydrous CH_2Cl_2 and a catalytic amount of benzyltriethylammonium chloride (BTEACl).[15c] Given the volatility of 1-butene, b.p. −6.3°C, vigorous stirring with a standard laboratory overhead stirrer did not seem practical, and the reaction was conducted in a sealed pressure vessel with less than efficacious magnetic stirring. As KBr precipitated, magnetic stirring did little. Yet the reaction was successful to a useful degree. After several days at room temperature, and work-up and distillation, the product was obtained in ≈50% yield as a faintly light-yellow clear liquid, b.p. 62–68°C (17 mm Hg). The 80:20 mixture of product and unreacted $CHBr_3$ was easily separated by preparative GC on a XF-1150 column and characterized through NMR spectroscopy and GC-MS spectrometry.

Assignments for the ^{1}H NMR spectrum for adduct **7** (Figure 3) were clarified with the aid of two-dimensional ^{1}H–^{1}H and ^{1}H–^{13}C NMR methods. The ^{1}H spectrum had a double of doublets (J = 7.0, 10.0 Hz; 1H) centered at δ = 1.73, a very complicated multiplet region from δ = 1.63 to 1.45, an apparent triplet at δ = 1.2 (J = 7.0 Hz; 1H) and a methyl triplet at δ = 1.10 (J = 7.5 Hz). The ^{1}H–^{1}H COSY data placed the C**H**$_2$–CH_3 protons within the complex multiplet, at δ ≈ 1.61 and 1.51. The proton at low field correlated with protons at δ ≈ 1.53 and at 1.2. The geminal protons at C(3) of the cyclopropyl ring had quite different chemical shifts, at δ = 1.73 and 1.2.

The H–C(3) doublet of doublets for δ 1.73 was taken to be *cis* to H–C(1), based on its larger *cis* vicinal coupling constant, 10 Hz, relative to the geminal $H_2C(3)$ J value of 7.0 Hz.[16] The upfield apparent triplet, J = 7.0 Hz, centered at 1.20 ppm, was assigned to H–C(3) *trans* to H–C(1). The dramatically different chemical shifts characterizing the two H–C(3) protons, about 0.53 ppm, stem largely from shielding by the ethyl substituent. Precedents for this phenomenon are provided, for instance, by (2-bromoethyl)cyclopropane and ethyl cyclopropane, wherein the cyclopropyl CH_2 *cis* > *trans* chemical shift upfield differences are both 0.39 ppm.

The MS ions recorded for the dibromocarbene adduct **7** corresponded to ^{79}Br and ^{81}Br patterns characteristic of dibromides $C_5H_8Br_2$ at *m/z* 226, 228, 230, $C_2H_2Br_2$ at 197, 199, 201, and $C_2H_2Br_2$ at 184, 186, 188. Two ion patterns for monobromides were evident for C_5H_8Br at 147, 149 and for C_2H_2Br at 105, 107. The base peak came at *m/z* 67, a signature for C_5H_7. The fragmentation ion progressions followed two main sequences, $C_5H_8Br_2$ to $C_2H_2Br_2$ to C_2H_2Br and from $C_5H_8Br_2$ to C_5H_8Br to C_5H_7, all readily formulated by plausible structural representations.

Reducing the dibromide **7** with Ph_3SnD using catalytic 9-BBN at room temperature was efficient and convenient.[17] Product **1-d_2** was initially collected as a 1:1 mixture with THF in a cold trap as it volatilized from the reaction vessel, and was then purified to high homogeneity (99+%) by preparative GC using the β,β′-ODPN column.

Experimental

(2-^{13}C-1-Ethyl)cyclopropane (1-^{13}C)

To a dry round-bottomed flask was added Mg (410 mg, 16.9 mmol) and 15 mL of dibutyl ether. To the stirred mixture cooled to 0°C in an ice-water bath was added dropwise over 5 min a solution of 2.275 g (15.9 mmol) of $^{13}CH_3I$ in 10 mL of dibutyl ether. The reaction mixture was allowed to warm slowly to rt and stirred for 2 h, until the Mg was consumed. The Grignard reagent was carried on without purification.

To a round-bottomed flask was added 8.4 mL of 0.1 M Li_2CuCl_4 in THF (0.8 mmol) and 1.0 g (7.4 mmol) of (bromomethyl)cyclopropane. An argon atmosphere covered the THF solution and it was cooled to 0°C. The Grignard reagent in dibutyl ether prepared immediately above was added dropwise over a 1-h period to the THF solution. The reaction mixture was stirred at 0°C for 2 h, fitted with a reflux condenser and cold trap, and then heated at 40°C for 4 h. Distillation gave a single fraction containing a ≈ 1:1 solution of **1-^{13}C** and THF. Preparative GC on a 0.64 cm × 3.0 m 20% β,β′-ODPN Chromosorb W-AW-DMCS column at 46°C, followed by collection in a glass cold trap equipped with suitable stopcocks (Figure 2) as it was kept at −131°C by a pentane/liquid nitrogen bath, gave 208 mg (40%) of **1-^{13}C** of greater than 98% homogeneity by capillary GC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (multiplet, 2H), 0.96 (t, J = 6.9 Hz, 3H), 0.70 to 0.58 (multiplet, 1H), 0.37 (dt, J = 4.2, 1.5 Hz, 2H), 0.00 (dt, J = 4.2, 1.5 Hz, 2H). A second preparation and purification afforded 118 mg of **1-^{13}C**. These two samples, and other samples of labeled ethylcyclopropanes, were transferred into separate 5 mL tube-shaped sample flasks equipped with high vacuum stopcocks for storage and shipping.

(2-d_3-1-Ethyl)cyclopropane (1-d_3)

To a dry round-bottomed flask was added Mg (410 mg) and 15 mL of dibutyl ether. The Grignard reagent derived from CD_3I was prepared as described above. The 0.1 M solution of Li_2CuCl_4 in 8.4 mL of THF, CD_3MgI in dibutyl ether, and (bromomethyl)-cyclopropane were utilized as described above to couple the Grignard reagent and alkyl bromide.

After the reaction was complete, distillation afforded a single fraction containing ≈30% product and 70% THF. Preparative GC as described above gave 101 mg (19% yield) of **1-d_3** in better than 98% purity by capillary GC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 2H), 0.72 to 0.58 (multiplet, 1H), 0.39 (dt, J = 3.6, 1.8 Hz, 2H), 0.00 (dt, J = 3.6, 1.8 Hz, 2H). MS (EI): m/z = 73 ($C_5H_7D_3$ M^+, strong), 55 ($C_4H_7^+$). Another preparation and purification by preparative GC provided 75 mg of additional **1-d_3**.

2,2-Dibromo-1-ethylcyclopropane (7)

The preparation of **7** was accomplished following the protocol described in the literature [15c] and sketched above. Distillation of the crude reaction mixture generated by the addition of dibromocarbene to 1-butene was obtained in 40% yield, a significant improvement over the literature precedent.[14] Isolation and purification using a 0.64 cm × 2.0 m XF-1150 column at 120°C afforded **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (dd, J = 7.0, 10.0 Hz; 1H), 1.63–1.45 (complex multiplet, 3H), 1.2 (t, J = 7.0 Hz, 1H), and 1.10 (t, J = 7.5 Hz, 3H) (compare [14] ^{1}H NMR); ^{13}C NMR (125.78 MHz, $CDCl_3$) δ 33.26, 29.63, 28.71, 26.35, and 12.92. MS (EI): m/z (%) = 226, 228, 230 (M^+, 1:2:1, weak), 199 ± 2 (20), 186 ± 2 (90), 147, 149 (32), 105,107 (19), 67 (100).

2,2-d_2-1-Ethylcyclopropane (1-d_2)

To approximately 2.0 g of a 4:1 solution of 2,2-dibromo-1-ethylcyclopropane (**7**) and $CHBr_3$ (≈7 mmol of **7**) diluted with 50 mL of THF at 0°C was added 9-BBN (90 mg, 0.7 mmol) followed by Ph_3SnD (5.8 mL, 21.5 mmol). The reaction solution was stirred at 0°C for 2 h and then allowed to warm to RT and stirred overnight. Distillation gave the d_2-labeled product together with considerable THF. Preparative GC separation of product from THF on a β,β′-ODPN column gave **1-d_2** (100 mg, ≈20% yield) of greater than 99% homogeneity by capillary GC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (multiplet, 2H), 0.96 (t, J = 6.9 Hz, 3H), 0.70–0.58 (multiplet, 1H), 0.37 (multiplet, 1H), −0.01 (multiplet, 1H). A second preparation and purification gave another 258 mg of **1-d_2.**

Conclusions

The preparations of labeled ethylcyclopropanes **1-^{13}C**, **1-d_3**, and **1-d_2** in high purity provided ample quantities, 860 mg in all, to make possible detailed studies of the reactions of these isotopomers of ethylcyclopropane leading to isotopomers of butadienes and methanes. Through shock-tube reaction techniques and suitable spectroscopic analyzes the mechanistic aspects of the fragmentation reactions involved should be accessible. Attempts to progress toward that goal are underway.

The two novel synthetic modifications of standard procedures and equipment that proved important in this work, the blending of CH_3MgI prepared in dibutyl ether with a solution of Li_2CuCl_4 in THF to facilitate the coupling of a CH_3MgI iodide with an alkyl bromide, and the improved collecting arrangements to capture the volatile and aerosol-prone ethylcyclopropanes as they exited the hot TC detector port of a preparative GC instrument, will be of utility in other investigations and synthetic applications. That realization will come in future work; in the present synthetic efforts, they proved essential.

Acknowledgement

We thank the National Science Foundation through CHE-0240104 and CHE-0514376 for financial support of this work, Dr. Richard C. Burrell for valuable assistance in the early phases of this synthetic effort, and Professor David K. Lewis, Connecticut College, for stimulating discussions.

References

[1] S. M. Tanatar, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1297–1300.
[2] L. Birladeanu, *J. Chem. Educ.* **1998**, *75*, 603–606.
[3] J. P. Chesick, *J. Am. Chem. Soc.* **1960**, *82*, 3277–3285. See also D. W. Setzer, B. S. Rabinovitch, *J. Am. Chem. Soc.* **1964**, *86*, 564–569.
[4] M. L. Halberstadt, J. P. Chesick, *J. Phys. Chem.* **1965**, *69*, 429–438.
[5] H. M. Frey, D. C. Marshall, *J. Chem. Soc.* **1965**, 191–194.
[6] S. W. Benson, H. E. O'Neal, *Kinetic Data on Gas Phase Unimolecular Reactions*. National Standard Reference Data Series, National Bureau of Standards 21, Washington, DC. **1970**, pp. 231–234.
[7] M. R. Willcott, R. L. Cargill, A. B. Sears, *Prog. Phys. Org. Chem.* **1972**, *9*, 25–98.
[8] D. K. Lewis, T. Gray, V. Katsva, K. Parcella, J. Schlier, B. L. Kalra, J. Cho, D. Mish, *Int. J. Chem. Kinetics* **2006**, *38*, 483–488.
[9] A. S. Thompson, In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3 (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 1957–1960.
[10] (a) C. H. Herr, F. C. Whitmore, R. W. Schiessler, *J. Am. Chem. Soc.* **1945**, *67*, 2061–2063. (b) R. Van Volkenburgh, K. W. Greenlee, J. M. Derfer, C. E. Boord, *J. Am. Chem. Soc.* **1949**, *71*, 172–175. (c) P. Pomerantz, A. Fookson, T. W. Mears, S. Rothberg, F. L. Howard, *J. Res. Natl. Bur. Standards* **1954**, *52*, 59–65.
[11] A. D. Pajerski, J. E. Chubb, R. M. Fabicon, H. G. Richey, *J. Org. Chem.* **2000**, *65*, 2231–2235.
[12] T. Leigh, *Chem. Ind.* (*London*) **1965**, 426–427.
[13] In an excellent review article on alkyl Grignard reagents. In *Science of Synthesis*: *Category 1, Organometallics*. Thieme Verlag, Stuttgart, Germany, **2004**, 573–596. K. Oshima mentions that CH_3MgI in diethyl ether and dibutyl ether is commercially available.
[14] Ya. M. Slobodin, M. M. Dolgopol'skaya. *J. Org. Chem. USSR* **1971**, *7*, 1347.
[15] (a) W. R. Roth, T. Schmidt, H. Humbert, *Chem. Ber.* **1975**, *108*, 2171–2175. (b) W. E. Farneth, M. W. Thomsen, *J. Org. Chem.* **1982**, *47*, 4851–4855. (c) M. von Seebach, S. I. Kozhushkov, H. Schill, D. Frank, R. Boese, J. Benet-Buchholz, D. S. Yufit, A. de Meijere, *Chem. Eur. J.* **2007**, *13*, 167–177.
[16] K. B. Wiberg, D. E. Barth, P. H. Schertler, *J. Org. Chem.* **1973**, *38*, 378–381.
[17] V. T. Perchyonok, C. H. Schiesser, *Tetrahedron Lett.* **1998**, *39*, 5437–5438.